REMARKS

Upon entry of the amendment, claims 13-65 are pending in the application. Support for the amendments to claim 13 can be found in the specification on p. 14, line 18 through p. 15, line 8. Support for the amendments to claims 14-16, 20-22, 43, and 49 can be found in the specification on p. 1, lines 7-9 and p. 10, line 8. Support for the amendments to claims 42 and 48 can be found in the specification on p. 11, lines 8-16; p. 13, lines 18-35; p. 14, line 12 through p. 15, line 8; and in original claim 11. Support for the amendments to claims 44-47 and 50-53 can be found in the specification on p. 1, lines 7-9; p. 10, line 8; and p. 14, lines 32-35. Support for new claim 60 can be found in the specification on p. 1, lines 7-9; p. 10, line 8; p. 11, lines 8-16; p. 12, line 8; p. 13, lines 21-22 and 28-31; p. 14, line 12 through p. 15, line 8; and in original claims 11 and 12. Support for new claims 61-63 can be found in the specification on p. 12, lines 11-15. Support for new claims 64 and 65 can be found in the specification on p. 14, lines 32-35.

I. Office Action Dated October 22, 2003

A. 35 U.S.C. 112, First Paragraph Rejection – Written Description

Reconsideration is requested of the rejection of claims 11, 13-16, 20-22, and 42-54 under 35 U.S.C. §112, first paragraph, on the asserted basis that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors were in possession of the claimed invention at the time the application was filed.

With this amendment, claims 11 and 54-59 have been canceled, and therefore, the rejection as applied thereto is rendered moot. Moreover, the bases for the Office's rejection of claims 11 and 54-59 would not support a similar rejection of claims 13-16, 20-22, 42-53, and 60-65.

"Compliance with the written description requirement is essentially a fact-based inquiry that will '**necessarily vary** depending on the **nature of the invention** claimed.'" *Enzo Biochem, Inc. v. Gen-Probe Inc.*, 296 F.3d 1316, 1324 (Fed. Cir. 2002)(citing *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1563 (Fed. Cir. 1991))(emphasis added).

The standard is whether the description allows persons of ordinary skill in the art **to recognize** that the inventor had possession of the claimed invention at the time of filing. *In re Alton*, 76 F.3d 1168, 1175 (Fed. Cir. 1996) (emphasis added); *see also*, *Vas-Cath*, 935 F.2d at 1557.

The Office has indicated that the present claims lack written description support to reasonably suggest that applicant was in possession of compositions that comprise either crude preparations of anionic dyes or ammonium salts thereof, regardless of their absorbance, in colors other than the specific red dyes.[1] The Office further asserts that the specification lacks written description support for compositions having specified optical or physical densities

1. Dye Selection

In the specification, applicants identify anionic tracer dyes, generically, as a component of their reagent. No particular color or family of dyes was described as being critical. Rather, "any color dye which is visible during the post-reaction analysis can be used; preferred are dyes which have a peak visible absorbance wavelength at between 430 and 617 nm; most preferably dyes have a peak visible absorbance wavelength at between 500 and 535 nm."[2] To exemplify their invention, applicants prepared a reagent containing a tracer having, for aesthetic reasons only, a particular shade of red.

Consistent with applicants' generic disclosure, persons of ordinary skill would have understood that applicants were similarly in possession of other colors. That is to say, persons of ordinary skill would have understood from applicants' disclosure and Examples that applicants could have arbitrarily selected a color other than red. Indeed, the prior art discloses the use of dyes imparting other colors as tracers. For example,

---

[1] The Office asserts that "only four dyes, Acid Red 4, Acid Red 1, Amaranth, and Acid Violet 5 were found to be suitable." *See*, Office Action dated October 22, 2003, p. 5, paragraph 8.

[2] Specification, p. 13, lines 12-17.

Köster et al.[3] disclose the use of fluorescent dyes generally and JOE, FAM, TAMRA, and ROX specifically in methods and kits for amplifying nucleic acid sequences. Likewise, Hopp et al.[4] disclose the use of dyes such as cresol red and tartrazine in PCR mixtures. Hopp et al. even used yellow food coloring purchased from a local grocery store.[5] While these artisans did not prepare reagents corresponding to those claimed by applicants, a person in the art would recognize from the knowledge and skill in the art and applicants' generic disclosure that applicants were in possession of much more than the particular combination of dyes selected in the Examples.

2. Optical Density

Optical density is merely a measure of the transmittance of a composition. As applied in this instance, optical density is merely a surrogate measure of the concentration of the tracer dye in the reagent. Accordingly, an increase in tracer dye concentration leads to an increase in optical density and *vice versa*.

According to their specification, applicants prefer compositions having an optical density of between about 5 and about 500.[6] In their Example 1, applicants exemplify the preparation of a composition having an optical density ***near the middle of this range***, *i.e.,* of 300, using 80% acid red 1 and 20% acid violet 5.[7] Since optical density is a ***measure of concentration***, applicants could have prepared a composition having a lesser optical density simply by incorporating less of the dye in the composition or, alternatively, could have prepared a composition having a greater optical density simply by incorporating more of the dye in the composition. In view of this disclosure, a person

---

[3] Köster et al., U.S. Patent No. 5,928,906 (discussed in greater detail in Section I.B., below).

[4] BioTechniques, 12(5): 679-680 (1992) (discussed in greater detail in Section II.A., below).

[5] Hopp et al., p. 679, column 2.

[6] Specification, p. 13, lines 27-31.

[7] Specification, p. 30, lines 1-6.

of ordinary skill clearly would have understood that persons of ordinary skill were in possession of compositions having an optical density of at least about 5 to about 500. This fact is reflected in the Interview Summary dated April 28, 2004 (summarizing the telephone interview of the April 20, 2004) issued by the Office, wherein Examiner Sisson "noted that claim 42 fairly encompassed virtually any optical density yet the specification provides written description for a range of from 5 to 500, which independent claims 48 and 60 recite."[8] Accordingly, claim 42 has been amended so that it now too recites the specific optical density of about 5 to about 500.

3. Physical Density

To assist in the addition of the reaction mixture to the analytical process, the density (*i.e.*, physical density) of the reaction mixture should be at least about 0.01 g/cm^3 greater than the density of the liquid phase of the analytical process. Applicants describe the use of sugars, glycerol or betaine (trimethylglycine) for this purpose, with glycerol being preferred. A particularly preferred solute for increasing the density is glycerol, which at a concentration of 50% in water has a density of about 1.14 gm/cm^3.[9] A person of ordinary skill would have understood from applicants' disclosure that there would be no benefit derived from going to unusually great densities.

Moreover, since the solute used to increase the density of the reagent is mixed with the reagent, the upper limits of the physical density of the reagent will naturally be less than the density of the solute itself. Accordingly, a person of ordinary skill would have understood from applicants' disclosure that the reagent would have a physical density with an upper limit of less than the density of the solute itself.

All of this taken together, a person of ordinary skill would have understood from this disclosure that applicants considered their invention to include compositions having a range of densities, that applicants had provided persons of ordinary skill with the

---

[8] Interview Summary dated April 28, 2004 (summarizing the telephone interview of the April 20, 2004), page 3.

[9] Specification, p. 15, lines 4-6.

means to control density (by including an appropriate density increasing solute), that they had exemplified a reagent having a density of 1.14 gm/cm^3, and that then density of the reagent could not be greater than the density of the solute used in the reagent. As such, a person of ordinary skill would have understood applicants to be in possession of reagents having a density of at least about 1.01 gm/cm^3, but less than the density of the solute.[10]

Accordingly, independent claims 42, 48, and 60 have been amended to recite that the reagent has a physical density of at least about 1.01 g/cm^3, but less than the density of the solute.

B. 35 U.S.C. 103(a) Rejection

Reconsideration is requested of the rejection of claims 11, 13-16, 20-22, and 42-54 under 35 U.S.C. 103(a) as being unpatentable over Köster et al. (U.S. Patent No. 5,928,906) in view of Nardone et al. (U.S. Patent No. 6,117,986).

With this amendment, claims 11 and 54-59 have been canceled, and therefore, the rejection as applied thereto is rendered moot. Moreover, the bases for the Office's rejection of claims 11 and 54-59 would not support a similar rejection of claims 13-16, 20-22, 42-53, and 60-65.

Claim 42 is generally directed to an aqueous reagent for an *ex-vivo* polymerase reaction in which a nucleic acid polymer product complementary to a nucleic acid polymer template is prepared. The reagent comprises Taq DNA polymerase and an anionic tracer dye ***unbound to primer or nucleotides*** which visually has a red appearance and a peak visible absorbance wavelength at between 430 and 617 nm and a solute to increase the physical density of the reagent, the reagent having an optical density of about 5 to about 500 at a visible wavelength of maximal tracer absorbance and being ***free of the primer and the nucleic acid polymer template*** and having a physical density of at least about 1.01 g/cm^3, but less than the density of the solute.

---

[10] A composition with such characteristics is described in the specification at p. 14, line 26 through p. 15, line 8, including examples of suitable solutes.

Claim 48 is generally directed to an aqueous reagent for an *ex-vivo* polymerase reaction in which a nucleic acid polymer product complementary to a nucleic acid polymer template is prepared. The reagent comprises Taq DNA polymerase, an anionic tracer dye ***unbound to primer or nucleotides*** consisting essentially of acid red 1 and acid violet 5, and a solute to increase the physical density of the reagent, the reagent having an optical density of about 5 to about 500 at a visible wavelength of maximal tracer absorbance, being ***free of the primer and the nucleic acid polymer template***, and having a physical density of at least about 1.01 g/cm^3, but less than the density of the solute.

Claim 60 is generally directed to an aqueous reagent for use in forming a polymerase reaction mixture comprising a thermostable DNA polymerase, a nucleic acid polymer template, a primer, nucleotides, a detectible anionic tracer dye unbound to primer or nucleotides, and a solute to increase the physical density of the reagent. The reagent comprises the thermostable DNA polymerase, the detectible anionic tracer dye, and the solute but being ***free of the primer and the nucleic acid polymer template***, the reagent having an ***optical density of about 5 to about 500*** at a visible wavelength of maximal tracer absorbance and a physical density of at least about 1.01 gm/cm^3, but less than the density of the solute.

Köster et al. discloses compositions that comprise a dye and a DNA polymerase. Taq polymerase is disclosed in one particular embodiment. These compositions are used in a sequencing method to detect the presence of specific nucleotide sequences. However, Köster et al. do not disclose the use of an anionic tracer dye or the use of Acid Red 1 or Acid Violet 1 in their compositions; instead, they use a variety of other dyes.[11] Moreover, Köster et al. describe nucleotide and dye or primer and dye combinations wherein the dye is incorporated into the nucleotide or primer.[12]

---

[11]See, Example 1 of Köster et al.

[12] See, Köster et al., column 10, lines 24-25, 33-34, and 56-57; column 11, lines 10-11; and Example 1, column 12, lines 26-28, 33, 40, 48, 55.

Nardone et al. disclose labeled nucleotide phosphoramidites and methods of producing the same. Specifically, Nardone et al. disclose compositions comprising nucleotide phosphoramidite precursors, and in particular pyrimidines, ***covalently coupled*** to a quencher molecule (*i.e.*, the quencher molecule is incorporated into the nucleotide phosphoramidite precursors). This quencher nucleotide phosphoramidite is incorporated into a larger labeling oligonucleotide (thereby resulting in a dye labeled oligonucleotide) having a fluorescent dye at the 5' end of the oligonucleotide and used to detect specific nucleotide sequences. Nardone et al. further disclose that the quencher molecule can be either acid red 1 or acid violet 5. Significantly, however, Nardone et al. do not disclose the use of acid red 1, acid violet 5, or combinations thereof as detectible anionic tracer dyes. Instead, they use it as a quencher for another dye, a fluorescent dye, which serves as the tracer.

In combination, Köster et al. and Nardone et al. fail to render the claimed invention obvious. Köster et al. employ tracer dyes, but not one fitting the requirements of claims 42, 48, or 60. In addition, Köster et al. disclose nothing of significance concerning their dyes. Nardone et al. disclose the use of acid red 1 and acid violet 5, but only as a ***quencher*** for a fluorescent dye. As such, what would have motivated a person of ordinary skill to substitute Nardone et al.'s quencher for Köster et al.'s dye? The Office provides no reason and none is apparent on this record. Rather, it appears the Office engaged in an impermissible hindsight reconstruction of the claimed invention. In the absence of a motivation to combine the references, a *prima facie* case of obviousness has not been established.[13]

Moreover, as discussed in the telephone interview of April 15, 2004, both Köster et al. and Nardone et al. disclose the incorporation of a the dye into a nucleotide phosphoramidite or primer. The incorporation of the dye into the nucleotide phosphoramidite or primer results in the ability to label the same with a minimally low concentration of dye (*i.e.*, a low optical density) – so low in fact, that the dye would not reach an optical density of 5 as disclosed in this art. As a minimum optical density of 5

---

[13] MPEP §2142.

is required in independent claims 42, 48, and 60, owing to the fact that the dye is unbound to a primer or nucleotide, Köster et al. and Nardone et al., either individually or in combination, fail to teach each and every element of claims 42, 48, and 60. In the absence of such a teaching, a *prima facie* case of obviousness has not been established.[14]

Claims 13-16, 20-22, and 61-65, which depend from claim 60, claims 43-47, which depend from claim 42, and claims 49-53, which depend from claim 48, are patentable over Köster et al. in view of Nardone et al. for the reasons stated above with respect to claims 42, 48, and 60 and by reason of the additional requirements which they introduce.

II. Telephone Interview of January 14, 2004

During the interview of January 14, 2004, the Office asserted that claims 13-16, 20-22, and 42-59 were rejected under 35 U.S.C. 103(a) as being unpatentable over the combination of Köster et al. (U.S. Patent No. 5,928,906), Nardone et al. (U.S. Patent No. 6,117,986), Hopp et al. (BioTechniques, 12(5): 679-680 (1992)), and Gelfand et al. (U.S. Patent No. 5,407,800). For the reasons discussed in the telephone interview of April 5, 2004, and detailed below, the rejection is improper.

With this amendment, claims 11 and 54-59 have been canceled, and therefore, the rejection as applied thereto is rendered moot. Moreover, the bases for the Office's rejection of claims 11 and 54-59 would not support a similar rejection of claims 13-16, 20-22, 42-53, and 60-65.

The subject matter of claims 42, 48, and 60, as well as the contents of Köster et al. and Nardone et al., is discussed above in Section I.B.

Hopp et al. disclose gel-loading dyes compatible with PCR reactions. Specifically, they disclose PCR mixtures ***containing all reaction components*** to which a PCR compatible dye is added.[15]

---

[14] MPEP §2142.

[15] Hopp et al., p. 679, column 1 and Figure 1.

Gelfand et al. disclose methods for the replication and amplification of RNA sequences using thermoactive DNA polymerases. These methods involve the use of PCR master mixes which contain ***either, but not both,*** Taq polymerase (referred to as the "PCR plus Taq master mix") or 50% glycerol (referred to as the "PCR minus Taq master mix"). In addition, both the PCR plus Taq master mix and the PCR minus Taq master mix also contained a primer (DM151, referred to as the "PCR upstream primer").

For the reasons stated above in Section I.B., the combination of Köster et al. and Nardone et al. does not render the present invention obvious. Moreover, as discussed in the telephone interview of April 5, 2004, the defects of this combination are not cured by the addition of Hopp et al. and Gelfand et al. Specifically, Hopp et al. fail to disclose a reagent that is free of primer. This reference provides no motivation to one of skill in the art to create an aqueous reagent comprising both a thermostable DNA polymerase, an anionic tracer dye, and a solute to increase the physical density of the reagent ***in the absence of a primer.*** In the absence of a motivation to combine the references, a *prima facie* case of obviousness has not been established.[16]

Gelfand et al. fail to disclose the combination of a thermostable DNA polymerase and a solute. They disclose each individually, but not the two in combination. In the absence of such, this reference provides no motivation to one of skill in the art to create an aqueous reagent comprising both a thermostable DNA polymerase and a solute to increase the physical density of the reagent. In the absence of a motivation to combine the references, a *prima facie* case of obviousness has not been established.[17]

Furthermore, and in any event, the two references fail to teach or suggest each of the requirements of claims 42, 48, and 60. None of Köster et al., Nardone et al., Hopp et al., or Gelfand et al., either individually or in combination, disclose or suggest a composition having both a DNA polymerase and a solute, or a composition with an optical density of about 5 to about 500 at a visible wavelength of maximal tracer

---

[16] MPEP §2142.

[17] MPEP §2142.

absorbance. In the absence of such, a *prima facie* case of obviousness has not been established.[18]

Claims 13-16, 20-22, and 61-65, which depend from claim 60, claims 43-47, which depend from claim 42, and claims 49-53, which depend from claim 48, are patentable over Köster et al. in view of Nardone et al. for the reasons stated above with respect to claims 42, 48, and 60 and by reason of the additional requirements which they introduce.

III. Telephone Interviews of April 5 and April 6, 2004

During the telephone interview of April 5, 2004, the Office asserted that currently submitted claims 13-65 lacked novelty over Setterquist et al. (Nucl. Acids. Res., 24(8): 1580-1581 (1996)).

Setterquist et al. disclose an agarose encapsulated PCR reagent, the contents of which are disclosed in Table 1. The components of the reagent include dNTPs, primers, cresol red, Taq polymerase, and glycerol.

As discussed in the telephone interview of the following day, April 6, 2004, with this amendment claims 13-16, 20-22, 42-53, and 60-65 are being amended to exclude the presence of a primer. As such, Setterquist et al. fail to disclose each and every element of claims 13-16, 20-22, 42-53, and 60-65, and therefore, cannot anticipate these claims.

---

[18] MPEP §2142.

IV. Telephone Interview of April 20, 2004

A. 35 U.S.C. 102(e) Rejection

During the telephone interview of April 20, 2004, the Office asserted that currently submitted claims 13-65 lacked novelty under 35 U.S.C. 102(e) over Park et al. (U.S. Patent No. 6,153,412).

As demonstrated by the Declaration under 37 C.F.R. 131 of inventor Brian W. Ward, attached hereto as Exhibit 1, and notebook pages cited therein, attached hereto as Exhibit A, the presently claimed invention was reduced to practice prior to the December 7, 1998, filing date of Park et al. Since the presently claimed invention was reduced to practice prior to the filing date of Park et al., Park et al. is not prior art against the presently claimed invention. Accordingly, any rejection based upon Park et al. is obviated.

The Office also asserted that the phrase "an analytical liquid phase" as used in claim 13 was confusing. Without addressing the merits of the Office's position, with this amendment applicants have deleted such language from claim 13.

Additionally, the Office asserted that written description support exists only for a composition with an optical density of about 5 to about 500, and that because claim 42 lacks such a requirement, it is not supported by the specification. Without addressing the merits of the Office's position, with this amendment applicants have amended claim 42 to add the requirement that the reagent claimed therein have an optical density of about 5 to about 500.

V. Telephone Interview of April 21, 2004

During the telephone interview of April 21, 2004, applicants discussed their proposed amendments to claims 13 and 42 (which are being made of record with this amendment) and the possibility of filing an RCE with a 37 C.F.R. 131 declaration.

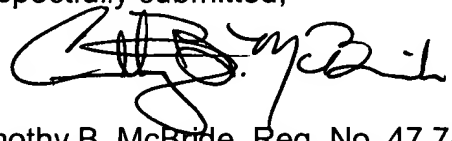
Moreover, as suggested by the Office, applicants respectfully request that the Office call the undersigned to discuss the present Amendment before issuing an Office with respect to the same.

CONCLUSION

In view of the foregoing, Applicants respectfully request reconsideration and withdrawal of the rejection of claims 11, 13-16, 20-22, and 42-59 under 35 U.S.C. 112, first paragraph, and 35 U.S.C. 103(a).

A check in the amount of $110.00 for a one month extension of time is enclosed. The Commissioner is hereby authorized to charge any additional fees which may be required to Deposit Account No. 19-1345.

Respectfully submitted,



Timothy B. McBride, Reg. No. 47,781
SENNIGER, POWERS, LEAVITT & ROEDEL
One Metropolitan Square, 16th Floor
St. Louis, Missouri 63102
(314) 231-5400

TBM/sxm